PCI, infarct size and aborted infarction

Determinants of final infarct size and incidence of aborted infarction in patients treated with primary coronary intervention and adjunctive abciximab therapy

Determinanten der endgültigen Infarktgröße und Häufigkeit des abortiven Infarkts bei mit Primär-PCI und zusätzlicher Abciximab-Therapie behandelten Patienten

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Summary
Aims: Assess the determinants of final infarct size in patients successfully treated with primary percutaneous coronary intervention (PCI) and abciximab therapy and check whether infarct abortion may occur. **Patients, methods:** In 208 patients we examined the parameters that predict final infarct size and the incidence of aborted infarction, defined by completely normal perfusion and regional wall motion plus > 50% left ventricular ejection fraction (LVEF) in gated single-photon emission computed tomography (SPECT) acquired at one month. **Results:** In linear regression analysis, sex ($p < 0.0001$), high cholesterol ($p < 0.05$), Killip class ($p < 0.0001$), symptom-to-reperfusion time ($p < 0.001$), admission ST segment elevation ($p < 0.0001$), infarct related artery ($p < 0.05$), and pre-procedural TIMI flow ($p < 0.002$) were significant univariate predictors of final infarct size. In multiple linear regression analysis, symptom-to-reperfusion time ($p < 0.001$), Killip class ($p < 0.0001$), ST segment elevation ($p < 0.003$), and sex ($p < 0.03$) remained significant predictors, model $R^2 = 0.53$. Aborted infarction was registered in 32 patients, more frequently female (59% versus 21%, $p < 0.00001$), older ($p < 0.02$), with larger prevalence of TIMI grade 3 ($p < 0.05$) and lower ST segment elevation at admission ($p < 0.05$). **Conclusions:** Sex, reperfusion delay, and initial infarct severity as indicated by Killip class and/or ST segment elevation appear the determinants of final infarct size in patients treated with primary PCI. The presence of aborted infarction seems related to the same factors and to preserved TIMI 3 flow.

Zusammenfassung
Ziel: Bestimmung der Determinanten der endgültigen Infarktgröße in Patienten, die erfolgreich mit Primär-PCI (perkutaner Koronarintervention) und Abciximab-Therapie behandelt wurden. **Patienten, Methoden:** In 208 Patienten untersuchten wir die Prädiktoren der endgültigen Infarktgröße und des Vorkommens eines abortiven Infarkts, der als Befund vollkommener normaler Durchblutung und regionaler Wandbewegung zusammen mit > 50% linksventrikulärer Ejektionsfraktion in nach einem Monate durchgeführter Gated Single-Photon-Emissionscomputertomographie definiert wurde. **Ergebnisse:** In Regressionanalyse, Geschlecht ($p < 0,0001$), erhöhter Cholesterinspiegel ($p < 0,05$), Killip Klasse ($p < 0,0001$), Zeit bis zur Rekanalisation ($p < 0,001$), ST-Strecken-Hebung bei der Aufnahme ($p < 0,0001$), Infarktarterie ($p < 0,05$) und prä-intervention TIMI-Fluss ($p < 0,002$) waren signifikante univariate Prädiktoren der endgültigen Infarktgröße. In Multivarianzanalyse, Zeit bis zur Rekanalisation ($p < 0,001$), Killip-Klasse ($p < 0,0001$), ST-Strecken-Hebung ($p < 0,003$) und Geschlecht ($p < 0,03$) blieben signifikante Prädiktoren, Modell $R^2 = 0,53$. Abortiver Infarkt wurde in 32 Patienten nachgeprüft, öfter weiblich (59% gegen 21%, $p < 0,00001$) und älter ($p < 0,02$), mit häufiger Vorhandensein eines TIMI-3-Flusses ($p < 0,05$) und niedriger ST-Strecken-Hebung bei der Aufnahme ($p < 0,05$). **Schlussfolgerung:** Geschlecht, Rekanalisationsverzögerung und anfängliche Infarktschwere, wie von Killip-Klasse und/oder ST-Strecken-Hebung bestimmt, scheinen die Determinanten der endgültigen Infarktgröße in mit Primär-PCI behandelten Patienten. Das Vorhandensein des abortiven Infarkts scheint mit denselben Faktoren und mit aufbewahrtem TIMI-3-Fluss zu entsprechen.

The aim of any reperfusion strategy in acute myocardial infarction is to reduce myocardial damage. Ideally, it should avoid any significant myocardial necrosis and the term aborted infarction has been used to describe this most positive outcome, which in patients submitted to fibrinolysis was defined by the finding of a minimal increase in cardiac enzymes together with a favourable evolution of the electrocardiographic modifications typical for acute myocardial infarction (5, 10, 11, 25, 30). Nowadays, however, the most advanced therapeutic regimen in acute myocardial infarction includes the execution of direct percutaneous coronary intervention (PCI) with adjunctive abciximab therapy (2, 28). The limitations of the enzymatic measurements of infarct size are well known, and can be particularly important in the presence of reperfusion (8, 29). Similarly, the electrocardiographic criteria used in the patients submitted to fibrinolysis are probably inadequate in the setting of primary PCI (4). The scintigraphic infarct size is a reliable surrogate endpoint for studies about different treatment strategies in acute myocardial infarction (7, 8). In patients without prior myocardial infarction, a completely normal perfusion pattern in myocardial scintigraphy should imply that no significant necrosis had taken place. Moreover, by using gated single-photon emission computed tomography (SPECT) it is possible to estimate with reasonable reliability the global left ventricular (LV) function and the regional wall motion and thickening (3, 6, 21). Therefore, a completely normal myocardial perfusion with infarct size equal to 0, together with a normal LV ejection fraction (EF) and

a normal regional wall motion and thickening in the follow up perfusion gated SPECT could be an alternative definition of aborted infarction. The aim of the present study was to evaluate the determinants of infarct size in acute myocardial infarction patients submitted to early PCI with direct stenting and adjunctive abciximab therapy and to identify the incidence and features of aborted infarction in this setting, using as reference the results of one-month follow up gated SPECT.

Patients, material, methods

Patients

The patient population included 208 consecutive acute myocardial infarction patients (152 men, 56 women, mean age 65 ± 12.4 years) submitted to primary PCI with stenting and adjunctive abciximab therapy. The inclusion criteria were: chest pain persisting more than 30 minutes associated with ST segment elevation of at least 0.1 mV in two or more contiguous electrocardiographic leads, admission within six hours of symptom onset, successful revascularization (defined as restoration of Thrombolysis In Myocardial Infarction (TIMI) trial (26) flow grade 3 and residual stenosis <30%). Patients were excluded if they had history of previous myocardial infarction, history of bleeding diathesis or allergy to abciximab, previous administration of fibrinolytic or abciximab therapy, major surgery within 15 days, and if informed consent could not be obtained.

Protocol

During the acute phase after admission, twelve-lead electrocardiography was repeatedly performed to assess the ST-segment. The single lead with the most prominent ST segment elevation before PCI was identified and ST segment elevation was measured at 60 ms after the J point in three successive QRS-T complexes. Resolution in ST segment elevation was defined at 30 min after infarct artery recanalization by an observer blind to the patient's clinical data (19).

Selective coronary angiography was performed in multiple projections before mechanical reperfusion. The presence of significant coronary obstruction was defined as >70% reduction in lumen diameter. Flow in the infarct-related artery was evaluated using the TIMI grade (26). Collateral circulation to the infarct-related artery was graded using the scoring scheme proposed by Rentrop (18). Immediately after diagnostic angiography, percutaneous coronary intervention with stenting of the infarct-related vessel was performed using standard material.

Creatine kinase (CK) measurements were systematically performed on admission and every three hours for the subsequent 24 hours, and then every 12 hours for two days.

The patients were studied at one month of index infarction for the assessment of myocardial perfusion and left ventricular function with gated SPECT.

Gated SPECT

Gated SPECT was acquired 60 min after the injection of 740 MBq of ^{99m}Tc-sestamibi, using a dual-head camera equipped with high-resolution collimators, 180° rotation arc, 32 projections, 60 seconds/projection, 8-frames/heart cycle, 64×64 matrices, 6.4 mm voxel size. Perfusion defects were quantified as percentage of LV wall, with the defect threshold set at 60% of peak uptake, according to an already described method (17, 21). Briefly, summed short axis slices were examined and three of them (basal, midventricular and subapical), were selected for defect quantitation (17). After identification of the epicardial profile by the operator, an automated program performed the circumferential analysis on 60 radii and identified those under the 60% uptake threshold. Finally, the uptake defects of the three slices were translated in the total infarct size, taking into account the slice diameter (17). LV end-diastolic and end-systolic volumes were calculated using the QGS program and LVEF was calculated from the left ventricular volumes as usual. (6) The cut off value to define normal the LVEF was set at >50% (1). Regional wall motion was visually assessed by an observer blind to patient identity and scored using a 4-point scale (1 = normal, 2 = hypokinesis; 3 = akinesis; 4 = dyskinesis) (3, 13).

Statistics

Values are presented as mean value ± standard deviation or as median and range as appropriate. Continuous variables were compared with ANOVA and categorical variables with Kruskall Wallis ANOVA. The comparison of proportions was made using the chi-square test with Yates' correction, as appropriate. The correlation between scintigraphic infarct size and the peak CK was calculated using Pearson's correlation coefficient. Multiple linear regression analysis was used to assess the determinants of final infarct size. The following parameters were examined: age, sex, diabetes, arterial hypertension, cholesterol level, smoking, pre-infarction angina, ST-segment elevation at admission, Killip class at admission, symptom-to-reperfusion time interval, extent of coronary artery disease, infarct related artery, collateral score and pre-procedural coronary TIMI flow grade. A p value <0.05 was considered statistically significant. We employed the Statistical Package for Social Sciences (SPSS, version 12.0)

Results

Determinants of infarct size

In one-month gated SPECT, the infarct size was 16.2 ± 14% (range 0–63.6%). This value significantly correlated with the enzymatic infarct size estimated by the peak CK: Pearson r = 0.65, p < 0.0001. The patient population was divided in the following tertiles according to the infarct size:
- small (2.3 ± 2.8%, range 0–8%),
- intermediate (14.2 ± 3.8%, range 8.2%–21%), and
- large infarction (32.5 ± 10.3%, range 21.3%–63.6%).

The three groups had significantly different one-month LVEF (56.2 ± 8.8%, 48.8 ± 10.2%, and 31.1 ± 9.9%, respectively, p <

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0.0001). As shown in Table 1, the three groups were significantly different in terms of sex distribution, incidence of high blood cholesterol, Killip class, ST segment elevation at admission, symptom-to-reperfusion time, pre-procedural TIMI flow and prevalence of left anterior descending as the infarct related artery. According to linear regression analysis, the following parameters were significant univariate predictors of final infarct size: sex ($p < 0.0001$), high cholesterol ($p < 0.05$), Killip class ($p < 0.0001$), symptom-to-reperfusion time ($p < 0.001$), ST segment elevation at admission ($p < 0.0001$), left anterior descending coronary artery as the infarct-related artery (IRA) ($p < 0.05$), and pre-procedural TIMI flow grade ($p < 0.002$). When these variables were included in a multiple linear regression analysis model, however, the significant predictors were only

- symptom-to-reperfusion time ($p < 0.001$),
- Killip class ($p < 0.0001$),
- ST segment elevation at admission ($p < 0.003$), and
- sex ($p < 0.03$).

The overall R^2 of the model was 0.53.

Aborted infarction patients

The criteria of aborted infarction were registered in 32 out of 208 patients (15%). Of them, 11 patients only had also a peak CK value <2 times the upper limit of normal. However, none of the patients with any degree of significant perfusion defect (infarct size >0) had a peak CK value <2 times the upper limit of normal. As regards the ST segment elevation resolution, a ≥50% decrease early after reperfusion was registered in 28 patients fulfilling the scintigraphic definition of aborted infarction and in 138 of the remaining subjects (NS). Table 2 compares the 32 patients with aborted infarctions with the remaining 176 patients. Patients with aborted infarction were more frequently female and were older. Although the distribution of pre-procedural TIMI flow grade was not significantly different between patients with and without aborted infarction, there was a larger prevalence of TIMI grade 3 flows in the patients with aborted infarction (Fig. 1). The ST segment elevation at baseline was significantly lower in the patients with aborted infarction, and the difference became greater in the ST segment elevation after PCI, whereas the difference in the degree of ST segment elevation resolution did not reach the statistical significance. Patients with aborted infarction had a significantly lower peak CK level.

Discussion

Pre-procedural determinants of infarct size

Several studies have examined separately the influence of various clinical parameters or of different therapeutic regimens on the final infarct size in patients with acute myocardial infarction submitted to reperfusion therapy. In patients submitted to the same treatment, Mehilli et al. have recently demonstrated that female patients have a smaller infarct size than men (15). The same group demonstrated that the time-dependency of reperfusion results is influenced by the reperfusion modality, with patients submitted to PCI showing a better result even in case of more delayed treatment (20). The favourable effect of a preserved TIMI flow before PCI was shown by Leoncini et al and by Ndrepepa et al. (12, 16). However, scanty data are available about the interaction between the various determinants in a homogeneously treated population, in whom epicardial blood flow had been effectively restored. According to our results, male sex, high blood cholesterol, left anterior descending as the infarct-

Tab. 1 Characteristics of the patient population divided according to infarct size tertiles

parameter		small	intermediate	large	p value
age (years)		67.4 ± 12.7	63.8 ± 12.7	63.7 ± 11.7	NS
women		29 (41%)	20 (29%)	7 (10%)	<0.00001
systemic hypertension		33 (47%)	29 (42%)	34 (49%)	NS
total serum cholesterol >200 mg/dl		25 (36%)	22 (31%)	36 (52%)	<0.05
smoker		27 (39%)	19 (28%)	24 (35%)	NS
Diabetes mellitus		10 (14%)	11 (16%)	7 (10%)	NS
preinfarction angina		16 (23%)	9 (13%)	15 (22%)	NS
Killip class III–IV		1 (1%)	2 (3%)	13 (19%)	<0.001
symptom onset to reperfusion (minutes)		205 ± 85	218 ± 85	266 ± 85	<0005
infarct-related coronary artery	left anterior descending right left circumflex	31 (44%) 30 (43%) 9 (13%)	18 (26%) 39 (57%) 12 (17%)	39 (57%) 23 (33%) 7 (10%)	<0.005
coronary artery disease extent	one-vessel two-vessel three-vessel	38 (54%) 21 (30%) 11 (16%)	43 (62%) 16 (23%) 10 (15%)	38 (55%) 25 (36%) 6 (9%)	NS
collateral circulation grade	0 1 2 3	61 (87%) 5 (7%) 2 (3%) 2 (3%)	61 (89%) 7 (10%) 1 (1%) 0	62 (90%) 5 (7%) 2 (3%) 0	NS
preprocedural TIMI grade	0–1 2 3	48 (69%) 12 (17%) 10 (14%)	50 (73%) 12 (17%) 7 (10%)	59 (85%) 10 (15%) 0	< 0.02
ST segment	elevation before PCI (mV)	3.4 ± 1.8	3.5 ± 2.1	5.1 ± 2.7	<0.00001
	elevation after PCI (mV)	0.9 ± 0.9	1.1 ± 1.2	2.3 ± 1.9	<0.00001
	resolution	74 ± 27%	71 ± 33%	57 ± 24%	<0.001
peak CK (U/l)		1137 ± 860	2138 ± 1811	4173 ± 2608	<0.00001

related artery, absence of preserved pre-procedural TIMI flow, longer symptom-to-reperfusion time, higher Killip class, and higher ST-segment elevation are the determinants of a larger final infarct size in univariate analysis. In a multivariate model, gender, reperfusion delay, Killip class and ST segment elevation remain the only significant predictors of final infarct size. These results are partly in agreement with the above mentioned prior reports that examined separately the influence of pre-procedural variables on final infarct size. The favourable influences of female gender and of an early treatment were confirmed even in a multivariate linear regression model. On the other hand, we observed that two parameters that are related to the initial severity of myocardial involvement, such as higher Killip class and higher ST segment elevation, still remained significant predictors whereas the pre-intervention TIMI flow was any longer included in the predictive model. This is quite surprising, taking into account the demonstrated favourable role of preserved TIMI flow before PCI. (12, 16). However, in a most recent paper using delayed enhancement in magnetic resonance imaging to measure the infarct size, Thiele et al. observed that a poor pre-procedural TIMI flow was just a borderline predictor of infarct size >10% of the left ventricle, together with prolonged time-to-treatment and anterior infarct location (27). Moreover, only time-to-treatment, but not TIMI flow nor infarct location remained a significant predictor when the ST segment resolution was included in the model (27).

Aborted infarction after primary PCI

So far, the concept of aborted infarction had been used in the setting of fibrinolysis, mainly to evaluate the effectiveness of early treatment, possibly performed even before the patient's admission to the hospital (10, 11, 30). In those reports, the definition of aborted infarction relied on the finding of a minor rise in cardiac enzymes (usually a CK rise less than two times the upper limit of normal) together with typical evolutionary electrocardiographic changes (usually a

Tab. 2 Comparison of the patients with aborted infarction versus the remaining patients

parameter		aborted infarctions	other infarctions	p value
age (years)		69.8 ± 10.9	64 ± 12.5	<0.02
women		19 (59%)	37 (21%)	<0.00001
systemic hypertension		16 (50%)	80 (45%)	NS
total serum cholesterol >200 mg/dl		10 (31%)	73 (41%)	NS
smoker		9 (28%)	61 (35%)	NS
Diabetes mellitus		5 (16%)	23 (13%)	NS
pre-infarction angina		7 (22%)	33 (19%)	NS
Killip class III-IV		1 (1%)	15 (20%)	NS
aymptom onset to reperfusion (minutes)		219 ± 85	217 ± 85	NS
infarct-related coronary artery	left anterior descending	13 (41%)	75 (43%)	NS
	right	15 (47%)	77 (43%)	
	left circumflex	4 (12%)	24 (14%)	
coronary artery disease extent	one-vessel	18 (56%)	101 (57%)	NS
	two-vessel	7 (22%)	55 (31%)	
	three-vessel	7 (22%)	20 (11%)	
collateral circulation grade	0	28 (88%)	156 (89%)	NS
	1	2 (6%)	15 (8%)	
	2	1 (3%)	4 (2%)	
	3	1 (3%)	1 (1%)	
preprocedural TIMI grade:	0–1	22 (69%)	135 (77%)	NS
	2	4 (12%)	30 (17%)	(<0.05)
	3	6 (19%)	11 (6%)	
ST segment	elevation before PCI (mV)	3.2 ± 1.6	4.2 ± 2.4	<0.05
	elevation after PCI (mV)	0.8 ± 0.9	1.5 ± 1.6	<0.01
	resolution	76 ± 27%	66 ± 29%	NS
peak CK (U/l)		783 ± 496	2784 ± 2333	<0.00001

prompt decrease in ST segment elevation early after completion of fibrinolysis) (5, 10, 11, 25, 30). However, the definition of aborted infarction was not standardized (5). The incidence of aborted infarction in the largest study in patients treated with fibrinolysis was 13.3%, with an increase to 25% in the subgroup treated <1 hour of symptom onset (25). Similarly, in a first study about the effectiveness of prehospital diagnosis and treatment, the rate of aborted infarction increased from 4% in patients treated after hospital admission to 13% in the prehospital group (10). These values were confirmed in a subsequent study from the same group (11).

Fig. 1
Histogram showing the distribution of Thrombolysis In Myocardial Infarction (TIMI) flow before PCI in patients with aborted infarction (■) versus those with myocardial infarction (□).
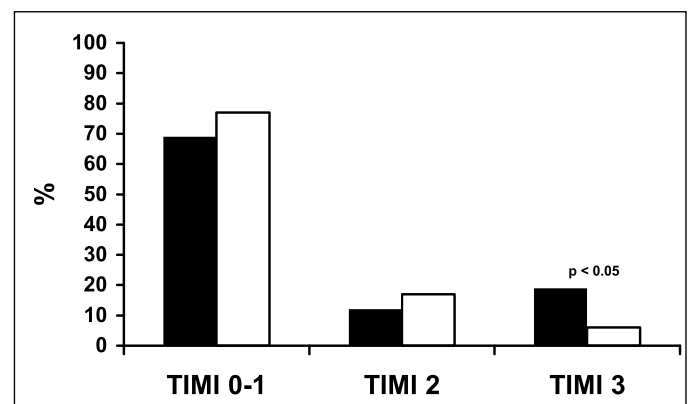
In our study, we used an alternative definition of aborted infarction, based on the finding of completely normal perfusion together with preserved regional and global function in follow up gated SPECT. The rationale for this choice is that the scintigraphic infarct size compares well with other estimates of myocardial damage, as confirmed by the good correlation with the CK peak observed also in our series. The scintigraphic infarct size is effectively used as surrogate end-point for assessing the efficacy of different therapeutic strategies in acute myocardial infarction patients (7, 8). Accordingly, the lack of any detectable perfusion defect would imply a most successful treatment. Furthermore, the possibility to accurately evaluate both regional and global left ventricular function through the gated SPECT technique reinforces the reliability of a scintigraphic definition of aborted infarction, taking into account the most favourable prognostic meaning of a normal left ventricular ejection fraction after myocardial infarction (9, 22). The simultaneous assessment of left ventricular function is as well helpful in identifying attenuation artefacts and allows to differentiate between a homogenous uptake pattern due to normal perfusion (in which regional and global LV function are normal) from one caused by diffuse and balanced perfusion abnormality (in which either regional wall motion and thickness or global LV function are most probably altered) (4, 23, 24).

According to our results, the incidence of aborted infarction in patients treated by primary PCI was 15%. The higher likelihood in patients with aborted infarction of being female and having an older age was confirmed, but we did not observe any difference in the coronary risk factor profile (25). With regard to the issue of treatment delay, however, it is remarkable that in spite of a generally longer time-to-treatment in our patient population in comparison to prior studies using fibrinolysis, the incidence of aborted infarctions was well comparable. This result is in agreement with prior observations comparing the time dependency of reperfusion results in patients submitted to PCI versus fibrinolysis (20). Our data would imply that primary PCI could be relatively more effective in obtaining infarct abortion than fibrinolysis so that the unavoidable delay due to the more complex procedure does not prejudice the possibility of escaping myocardial necrosis. According to our data, there is a higher incidence of re-established (TIMI grade 3) coronary flow before treatment. The other major difference between patients with and without aborted infarction is the larger extent of the potential necrosis before treatment, as suggested by the significantly higher ST segment elevation in the infarct exploring lead at admission. These findings are in agreement with what had been observed in patients submitted to fibrinolysis (25).

Limitations

The results of the study presented here must be evaluated taking into account its limitations. The patient population is comparable to that of other studies about the factors affecting the infarct size, but remains smaller than that of previous reports about aborted infarction in patients treated by fibrinolysis (10, 25). With regard to the assessment of infarct size determinants, the main limitation is the lack of scintigraphic data about the initial area at risk, which we could just infer indirectly from the Killip class and the ST segment elevation at admission. As regards the specific issue of aborted infarction, the most important limitation of this study is the arbitrary choice of a novel definition based on the results of follow up gated SPECT instead of on evolutionary ST segment changes and minimal enzymatic increase. It is undeniable that a direct comparison of the two criteria in a wide patient population would have been desirable. On the other hand, it must be admitted that the previous definition of aborted infarction was arbitrary as well, albeit reasonable and supported by follow up data of a better outcome in the patients who fulfilled it (5, 25). Moreover, there is a very large body of evidence supporting the value of the scintigraphic infarct size (7, 8). Also in our patient population, the correlation of scintigraphic infarct size with the enzymatic estimate represented by the CK peak was satisfactory. The reliability of myocardial perfusion imaging has been certainly increased by the introduction of gated SPECT (22). Some concern could still be present for the recognition of small non transmural infarctions. It is well known that preserved tracer uptake in subepicardial layers may prevent the recognition of subendocardial infarction in perfusion scintigraphy, and therefore magnetic resonance imaging is the optimal method for detecting non transmural necrosis (31). On the other hand, the simultaneous demonstration of normal global left ventricular function, normal regional wall motion, and preserved wall thickening makes quite unlikely that patients with important subendocardial scars were wrongly classified as aborted infarctions. Therefore, our definition of aborted infarction based on the presence in a relatively early follow up gated SPECT of a completely normal perfusion pattern together with LVEF > 50%, normal LV volumes, and normal regional wall motion appears reliable, at least in patients at their first myocardial infarction as in our population.

Conclusion

Our study indicates that sex, symptom-to-reperfusion time and clinical (Killip class) and electrocardiographic (ST segment elevation) parameters of initial infarct severity are the determinants of infarct size in patients admitted to the hospital within 6 hours of symptom onset and treated with primary PCI obtaining effective epicardial recanalization. Furthermore, it demonstrates that abortion of myocardial infarction is possible in these patients and that female gender, preserved TIMI 3 flow and less severe initial involvement as demonstrated by lower Killip class and ST segment elevation appear to be the factors most directly related to the achievement of infarct abortion.

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